Difficult Lesions in the Differential Diagnosis of Endocrine Tumors: Parathyroid Carcinoma

Ronald A. DeLellis, M.D.
Department of Pathology and Laboratory Medicine
The Warren Alpert Medical School of Brown University
and
The Rhode Island Hospital
Providence, Rhode Island 02903

Primary hyperparathyroidism (P-HPT) is now recognized as one of the most common of all endocrine disorders. When defined by clinical and pathological parameters, solitary adenomas account for 80-85% of cases of P-HPT, hyperplasias for 10-15% and carcinomas for less than 1% in the US and most Western European countries. However, the incidence of parathyroid carcinoma has been reported to be as high as 5% in Italy and Japan. Whether the relatively high incidence of parathyroid carcinoma in the latter countries is the result of true geographic differences or is related to differing pathological criteria is unknown.

While the diagnosis of parathyroid adenomas is usually straightforward, the diagnosis of parathyroid carcinoma is often challenging. Parathyroid carcinoma most often presents as a poorly circumscribed mass that is densely adherent to the surrounding soft tissues of the neck or to the thyroid gland. However, some carcinomas may be grossly encapsulated and may be impossible to distinguish from adenomas. In studies reported by Schantz and Castleman in the early 1970’s, important features of carcinoma included the presence of fibrous bands, mitotic activity, capsular invasion and vascular invasion. Fibrous bands were present in 90% of their cases and were characterized by the presence of acellular collagenous tissue that subdivided the tumor into irregularly shaped lobules. Fibrous bands, however, are not specific for carcinomas and may be present in large adenomas that have undergone degenerative changes.

Schantz and Castleman reported mitotic activity in 80% of carcinomas, but mitotic activity is also present in at least 70% of adenomas and hyperplasias (Snover and Foucar; San Juan et al). Atypical mitoses, on the other hand, appear to be a specific feature of parathyroid malignancies. Capsular invasion is present in at least 60% of carcinomas and is characterized by extension of tumor into the surrounding skeletal muscle, thyroid gland or perineural spaces. In order to qualify as bona fide capsular invasion, tumors must extend through the entire thickness of the capsule. True capsular invasion should be distinguished from entrapment of tumor cells within the capsule, which may be particularly prominent in adenomas that have undergone degenerative changes.
Vascular invasion was present in 10-15% of carcinomas in the series of Schantz and Castleman. The diagnosis of vascular invasion should be restricted to those cases in which the affected vessels are present within the capsule or within vessels in the surrounding soft tissues. Although vascular invasion is an uncommon feature of parathyroid carcinomas, it is virtually diagnostic of malignancy. Perineural space invasion is also uncommon in carcinomas, but similar to vascular invasion, it is diagnostic of malignancy.

Most carcinomas have a solid growth pattern with tumor cells arranged in diffuse masses, small nests or trabeculae. A few tumors may exhibit spindle cell, follicular or even papillary patterns. Many carcinomas exhibit mild variations in nuclear size and shape, but some may exhibit profound pleomorphism with coarse chromatin and macronucleoli. These features should be distinguished from the nuclear atypia encountered so frequently in parathyroid adenomas and other benign endocrine tumors (so-called "endocrine atypia"). Additionally, some tumors may show foci of necrosis, a worrisome finding in any parathyroid tumor.

Implantation of parathyroid tissue may occur following capsular rupture or incomplete excision of parathyroid adenomas. Differentiation of this phenomenon from recurrence of a previously resected (and undiagnosed) carcinoma is exceedingly difficult since both may be associated with significant fibrosis. Similarly, implantation of parathyroid tissue may occur following excision of hyperplastic parathyroid, a phenomenon that has been termed "parathyromatosis" (Reddick et al).

The term "atypical adenoma" has been used to describe a subset of tumors that share some of the features of parathyroid carcinomas (fibrosis, mitoses, questionable capsular invasion) but which lack definitive evidence of invasive growth. In this regard, the tumors are similar to those described by Bondeson et al as "equivocal". In a study of 24 tumors classified as atypical adenomas, mean tumor size was 2.2 cm and mean tumor weight was 6.5 grams (Guitert and DeLellis). The most common findings in this group were entrapping of tumor within the capsule (87%), intratumoral fibrosis (75%), prominent hemosiderin deposits (58%), cyst formation (50%), mitoses (30%) and peritumoral fibrosis (25%). Capsular invasion without extension of tumor beyond the capsule and intratumoral vascular invasion were each present in single cases, but none of the cases had evidence of necrosis. The average clinical follow-up in this group is now 7 years and none of the patients has developed tumor recurrence or metastatic disease. The findings in this study suggest that the behavior of atypical adenomas, as defined above, does not differ from that of adenomas of usual type.

Studies of the proliferative fractions of parathyroid tumors have revealed higher values in carcinomas and adenomas, but the overlap of values in equivocal cases has limited the value of this approach (Abbona et al). An additional approach has involved the use of antibodies to p27 which encodes a cyclin dependent kinase inhibitor. As compared with adenomas, carcinomas had a 3-fold decrease in p27 expression (Erickson et al). These findings have suggested that low p27 and high Ki-67 labeling indices may be helpful in the distinction of parathyroid adenomas and carcinomas. Stojadinovic and
coworkers have reported that the phenotype p27(+), bcl-2(+), Ki-67(-) and mdm2 (+) was present in 76% and 29% of typical adenomas and atypical adenomas, respectively, and in no cases of parathyroid carcinoma.

Although early molecular studies suggested a role for the RB gene in the development of parathyroid carcinomas (Cryns et al), more recent studies have concluded that neither RB nor BRCA2 are likely to act as classical tumor suppressor genes (Cetani et al; Shattuck et al). This conclusion does not rule out the possibility that decreased RB function in carcinomas, whether secondary or due to epigenetic effects, may play a role in tumor development. It is also possible that other genes present on chromosome 13 may be implicated in the development of parathyroid malignancies.

Mutations of the HRPT2 gene are responsible for the development of the hyperparathyroidism-jaw tumor (HPT-JT) syndrome which is inherited as an autosomal dominant trait (Carpten et al). The commonest manifestations include primary hyperparathyroidism fibro-osseous lesions of the mandible and maxilla and a variety of renal lesions. Hyperparathyroidism in affected patients occurs as a result of neoplasms of one or more parathyroid glands which frequently show cystic change. Interestingly, parathyroid carcinomas occur in 10-15% of patients with the HPT-JT syndrome.

The role of the HRPT2 gene in the pathogenesis of sporadic parathyroid carcinomas was first demonstrated by Howell et al in 2003. Shattuck subsequently demonstrated HRPT2 mutations in 10 of 15 patients with sporadic parathyroid carcinoma. Interestingly, the HRPT2 mutations in some of these patients were identified as germline mutations. The latter finding suggests that a subset of patients with apparent sporadic parathyroid carcinomas carry germline mutations in the HRPT2 gene and may, in fact, have the HPT-JT syndrome or a variant of that syndrome. The findings further suggest that: 1) all patients with parathyroid carcinoma should have jaw and renal imaging studies; 2) patients with parathyroid carcinoma should be tested for HRPT2 mutations.

Loss of parafibromin has been reported as a marker for parathyroid carcinoma (Tan et al). These workers noted that loss of parafibromin nuclear staining had a 96% sensitivity and 99% sensitivity for the definitive diagnosis of parathyroid carcinoma. In addition to parafibromin loss in carcinomas, this protein was also absent from HPT-JT associated adenomas. Similar results have been reported by Gill et al and Juhlin et al. However, in our experience, loss of parafibromin staining has been noted in a subset of adenomas unassociated with the HPT-JT syndrome while some carcinomas have shown positive staining (Mangray et al). The studies of Khanafshar et al suggest that loss of HRPT2 with diffuse strong positivity for galectin-3 is characteristic of parathyroid carcinomas.
References


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